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### Permalink

<https://escholarship.org/uc/item/4528g98g>

### Journal

ACS omega, 4(5)

### ISSN

2470-1343

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### Publication Date

2019-05-01

### DOI

10.1021/acsomega.9b00592

### Supplemental Material

<https://escholarship.org/uc/item/4528g98g#supplemental>

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Journal:	ACS Omega
Manuscript ID	Draft
Manuscript Type:	Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Huang, Po-Ju; University of California Santa Barbara, Chemistry and Biochemistry garcia, john; University of California Santa Barbara, chem and biochem Fenwick, Aidan; University of California Santa Barbara Department of Chemistry and Biochemistry, Department of Chemistry Wu, Guang; University of California Santa Barbara Department of Chemistry and Biochemistry, Chemistry Ford, Peter; University of California Santa Barbara Department of Chemistry and Biochemistry, Department of Chemistry

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# Nitric Oxide Uncaging from a Hydrophobic Chromium(III) PhotoNORM. Visible and Near Infrared Photochemistry in Biocompatible Polymer Disks.

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**ABSTRACT:** Devices consisting of polymer disks (PDs) of optically clear or translucent, medical grade silicone loaded with a new hydrophobic, oxygen-stable, photo-activated nitric oxide releasing moiety (photoNORM) are described. The photoNORM is the new O-nitrito chromium(III) complex *trans*-[Cr(PetA)(ONO)<sub>2</sub>](BF<sub>4</sub>) (PetA = 5,14-dimethyl-7,12-diphenyl-1,4,8,11-tetraazacyclotetra- decane) of which the synthesis, x-ray crystal structure and solution phase photochemistry are described. Several different commercially available silicone polymers were tested with this photoNORM and nitric oxide photo-uncaging with 451 nm light from these systems is compared. In addition, PDs were loaded with the photoNORM and neodymium-sensitized upconverting nanoparticles (Nd-UCNPs). The Nd-UCNPs absorb NIR light at ~800 nm and activate NO release from the *trans*-[Cr(PetA)(ONO)<sub>2</sub>]<sup>+</sup> cation. The use of such ensembles as implants provide a potential strategy for the *in vivo* uncaging of NO at physiological targets triggered by tissue-transmitting NIR excitation. Also reported are the x-ray crystal structures of *cis*- and *trans*-[Cr(PetA)Cl<sub>2</sub>]Cl.

<sup>‡</sup>These researchers contributed equally to the experimental studies described.

## Introduction

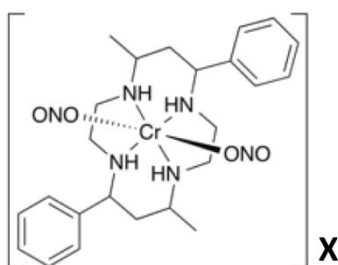
There has been considerable recent interest in developing strategies for photolysis induced release (photo-uncaging) of various bioactive small molecules at physiological targets for potential therapeutic applications.<sup>1-11</sup> One such molecule is the promiscuous bioregulator nitric oxide (NO), which plays important roles in mammalian cardiovascular and neuro-biology as well as immune response<sup>12,13</sup> and which, among other properties, displays antibacterial activity in combating biofilms.<sup>14</sup> This combination has drawn attention from this laboratory<sup>15-17</sup> and others<sup>18-25</sup> to the design and study of photo-activated NO releasing moieties (photoNORMs). The advantages of photo-uncaging include exquisite control of the timing, location and dosages of delivery. However, two disadvantages come immediately to the forefront. The first is the difficulty in localizing the caged bioactive molecule at the desired target area where release can be triggered with light. The other is the rather poor transmission of ultraviolet and visible wavelength through mammalian tissue with the exception of the relatively narrow window falling at long visible and shorter near-infrared (NIR) wavelengths.<sup>26</sup> Not only do shorter wavelengths penetrate poorly, the resulting tissue heating from the absorption of those wavelengths can lead to collateral damage.

One approach to targeted placement at a specific site is to incorporate the bioactive compound into a solid matrix (for example, a biocompatible polymer) that can be used as an implant.<sup>27-30</sup> Implants are already used for timed drug release,<sup>31</sup> but one using a caged precursor allows release only upon demand and provides dosage control by the amount of light used.<sup>32</sup> Such an device could be attached to an optical fiber that would transmit light to the target site to uncage the desired bioactive molecule. Alternatively, if the device were responsive to NIR excitation, then the use of the fiber and associated hardware may be unnecessary.

In this context, we previously described devices consisting of mm-sized polydimethylsiloxane (PDMS) polymer disks (PDs) containing upconverting nanoparticles (UCNPs) and infused with Roussin's black salt  $\text{Na}[\text{Fe}_4\text{S}_3(\text{NO})_7]$  (RBS).<sup>33</sup> UCNPs serve as antennas to effect NIR-to-visible (or UV) up-conversion by *sequential* multi-photon excitation at 980 nm with the lanthanide ion  $\text{Yb}^{3+}$  as the light absorbing sensitizer and a second lanthanide ion ( $\text{Er}^{3+}$  or  $\text{Tm}^{3+}$ ) as the emitter of visible and/or UV wavelengths after energy transfer from the sensitizer.<sup>34-38</sup> The

upconverted light emitted from the UCNP was reabsorbed by the RBS leading to photo-induced NO release from this photoNORM.<sup>39</sup> The advantage of UCNP is that upconversion requires much lower excitation intensities than does simultaneous two photon excitation, so one can use a relatively simple diode laser operating at 980 nm to effect multiphoton excitation of the UCNP leading to NO release.<sup>34</sup> Furthermore, we demonstrated that NIR excitation triggered photo-uncaging from these RBS-containing devices even through tissue filters.<sup>33</sup>

Described here is an investigation of analogous devices based on PDs prepared from a series of different commercially available, medical grade, biocompatible silicone polymers with the goal of evaluating whether different formulations would affect the photochemical uncaging of NO. The photoNORM selected in these studies is the  $\text{BF}_4^-$  salt of the previously unreported chromium(III) complex cation  $\text{trans}[\text{Cr}(\text{PetA})(\text{ONO})_2]^+$  (PetACrONO), where PetA = 5,14-dimethyl-7,12-diphenyl-1,4,8,11-tetraazacyclotetradecane, the synthesis of which is described. The PetACrONO salt is photoactive toward NO release in solution, is hydrophobic and is readily infused into PDs prepared from these polymers. Nitric oxide uncaging from the resulting devices can be activated by visible light excitation.



**PetACrONO**

Also described are PDs prepared both with PetACrONO and with this photoNORM and neodymium(III) doped  $\beta\text{-NaYF}_4\text{:Tm/Nd/Yb/Gd@NaYF}_4\text{:Nd}$  UCNP (Nd-UCNP).<sup>40,41</sup> The advantage of Nd-UCNP is that these can be excited with a continuous NIR diode laser operating at  $\sim 800$  nm<sup>42,43</sup> and the resulting upconverted visible light is reabsorbed by the photoNORM to uncage NO. Excitation at  $\sim 800$  nm allows one to avoid the modest absorbance by water at 980 nm, thereby improving NIR transmission depth and reducing potential tissue damage due to heating

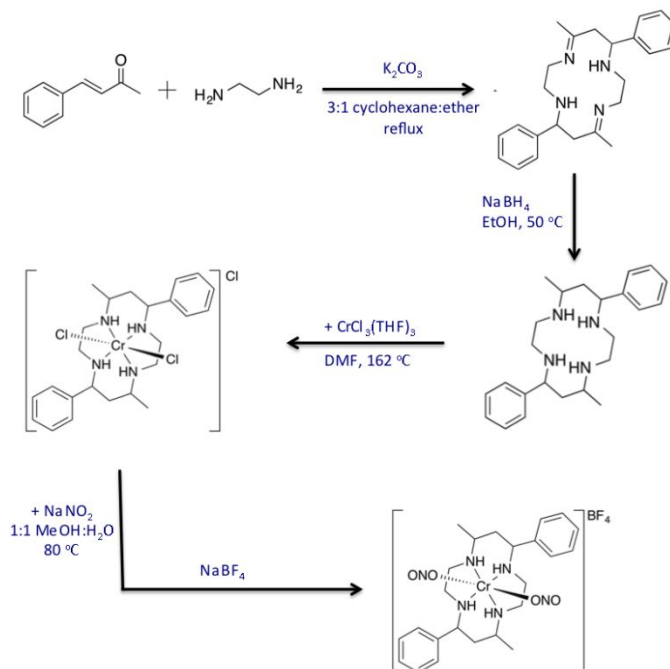
effects. During the course of the experiments described here, Ostrowski and coworkers,<sup>30</sup> reported the NIR-induced release of NO from several polysilicone composites containing the well-studied<sup>44,45</sup> photoNORM *trans*-[Cr(cyclam)(ONO)<sub>2</sub>]<sup>+</sup>X<sup>-</sup> ("CrONO", cyclam = 1,4,8,11-tetraazacyclotetradecane, X<sup>-</sup> = BF<sub>4</sub><sup>-</sup> or BPh<sub>4</sub><sup>-</sup>) and UCNPs that are activated by visible and by 980 nm excitation.

## Experimental Section

**Materials:** The NaYF<sub>4</sub>:Yb/Tm/Nd/Gd (30/0.5/1/20 mol %)/NaGdF<sub>4</sub>:Nd (20 mol %) core-shell UCNPs (Nd-UCNPs) used in these studies were provided by Dr. E. M. Chan and E. S. Levy at the Molecular Foundry of the Lawrence Berkeley National laboratory. The biocompatible silicone polymers used included NuSil Technology LLC formulations MED-4805, MED4-4220, MED-6019, MED-6215, MED-6233, and MED-6755. The NuSil<sup>TM</sup> silicones were gifts from the Allergan Corporation and from NuSil Technology LLC.

**Syntheses:** The synthesis of the PetACrONO salts is outlined in Scheme I. The ligand PetA was prepared by the NaBH<sub>4</sub> reduction of the unsaturated macrocycle 5,14-dimethy-7,12-diphenyl-1,4,8,11 tetraazacyclotetradeca-4,14-diene as described by Hideg and Lloyd.<sup>46</sup> The dichloro Cr(III) complex *trans*-[Cr(PetA)Cl<sub>2</sub>]Cl was prepared the reaction of PetA and CrCl<sub>3</sub>(THF)<sub>3</sub> in refluxing dimethylformamide as described by DeRosa for analogous macrocycles.<sup>47</sup> This procedure gives a mixture of the *cis*- and *trans*- complexes which was separated by chromatography on silica. For the reaction with PetA, the latter is favored (70% yield) over the less desirable *cis* form (10%) which could be converted to the *trans* form by refluxing in dichloromethane (DCM). The bis(O-nitrito) complex salt *trans*-[Cr(PetA)(ONO)<sub>2</sub>]BF<sub>4</sub> was synthesized from *trans*-[Cr(PetA)Cl<sub>2</sub>]Cl by procedures modified from those described for the cyclam analogs (Scheme 1).<sup>43</sup> Synthesis details and analytical data are reported in the Supporting Information (SI).

**X-ray Crystallography:** The solid state crystal structures of *trans*-[Cr(PetA)(ONO)<sub>2</sub>]BF<sub>4</sub> and of *cis*- and *trans*-[Cr(PetA)Cl<sub>2</sub>]Cl were determined by X-ray diffraction on a Kappa Apex II single-crystal diffractometer. X-ray structural data are summarized in SI Tables S1, S2 and S2.



**Scheme 1:** Synthetic sequence used to prepare *trans*-[Cr(PetA)(ONO)<sub>2</sub>] $\text{BF}_4$  (see SI for more details).

**Preparation and loading of polymer disks:** Procedures similar to those described previously<sup>33</sup> were used. The round PDs (10 mm diameter, 2 mm thick) were fabricated by mixing the monomer base (Part A) and the curing agent (Part B) in the weight ratios recommended by data sheets from the manufacturer NuSil Technology for the different formulations and then deaerated under vacuum in the antechamber of an inert atmosphere box for 30 min. An aliquot of this mixture ( $\sim 50\ \mu\text{L}$ ) was added to a custom-made mold (10 mm diameter, 2 mm height). Next, the PD was annealed at  $\sim 110^\circ\text{C}$  for  $\sim 1\ \text{h}$  then allowed to set at room temperature for at least 12 h. After fabrication, the PDs were removed from the mold and transferred into the glove box for infusion of the photoNORM. This was done by incubating the PD in a highly-concentrated ether solution of *trans*-[Cr(PetA)(ONO)<sub>2</sub>] $\text{BF}_4$  (15 mg/mL) for 5 min followed by vacuum drying. This was repeated 3 times. Finally, the dried PDs were washed multiple times with water to remove surface photoNORM that was not impregnated into the PD. This was repeated until none of the PetACrONO was detected in the wash solution. After several such washes, no leaching was evident in the solution spectra even after 24 h incubation in aqueous media. The resulting PDs were stored in the dark under an inert atmosphere until use. For PDs prepared for NIR studies, a

5 mg portion of the solid Nd-UCNPs was physically mixed with the polymer in the disk molds before curing.

**Photochemical studies: Solution phase studies.** Photolysis of PetACrONO was carried out in isobutyronitrile solution. The NO release was determined by entraining the photolysis solution contained in a "Y" cell with medical grade air which then flowed to a Sievers Nitric Oxide Analyzer (NOA, GE model NOA-280i), where it was detected and quantified via a calibrated chemiluminescence technique (SI Figure S1). (In each case, the entraining gas was purged through a solvent bubbler prior to entering the photolysis cell in order to reduce evaporative losses.) The photoexcitation source was either the 365 nm emission from a 200 W high pressure mercury lamp isolated with an interference filter or the 451 nm light from a Luxeon blue light emitting diode (LED) (SI Figure S2). Excitation intensities at 365 nm were determined by ferrioxalate actinometry,<sup>47</sup> while those at 451 nm were determined with a power meter (Newport Model 8442 PE).<sup>48</sup> Excitation intervals were controlled using a Uniblitz shutter, and quantum yields of NO release ( $\Phi_{\text{NO}}$ ) were determined by evaluating the NO released and recorded using the NOA software ("Liquid") for varied excitation intervals. The slope of a plot of NO released vs. total light absorbed by the solution gives  $\Phi_{\text{NO}}$  (SI Figure S3).

**Photoreactions in polymer disks:** The PDs were attached to a glass substrate using double sided tape that was then mounted into a flow cell where the photolysis was effected under streaming helium or medical grade air (SI Figure S1).<sup>32</sup> The NO released from the sample was transferred from the cell via the flowing gas to the NOA, where it was detected and quantified. The visible photoexcitation source was the royal blue (451 nm) Luxeon LED operating in the 45-500 mW range. The NIR photoexcitation source (794 nm) was a Sheaupac NIR fiber coupled diode laser module from ILX Lightwave. Incident photon flux during a photolysis was measured using a Newport Model 8442 PE optical power meter with a silicon photodiode detector. The photolysis laser beam (0.8 mm diameter) was oscillated by reflecting off two movable mirrors controlled by a Tektronix AFG320 arbitrary function digital generator as described previously (SI FigureS4).<sup>32</sup> The two mirrors each control the scanning width in one direction (horizontal or vertical), so that adjusting the individual oscillating frequencies defines the size of the scanned area. Experiments were run with mirror frequencies of 78.93 Hz and 48.93 Hz, which scanned the collimated laser

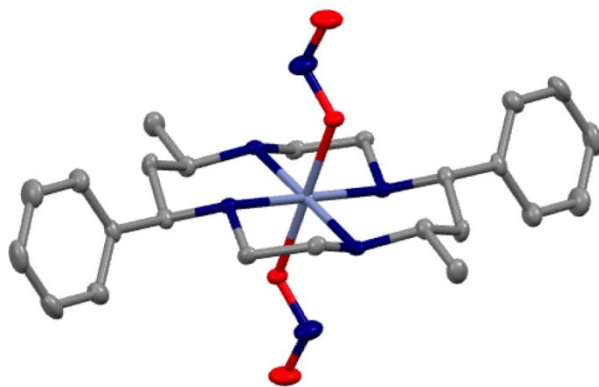


beam over most of the 10 mm diameter PDs in order to compensate for inhomogeneities in Nd-UCNP distribution in the polymer matrices while avoiding the damage that sometimes occurred when focusing on a single spot.<sup>32</sup> Excitation intervals were controlled by the Uniblitz shutter.

## Results and Discussion:

### ***Syntheses and structures of $\text{trans-[Cr(PetA)Cl}_2\text{]Cl}$ and $\text{trans-[Cr(PetA)(ONO)}_2\text{]BF}_4$ .***

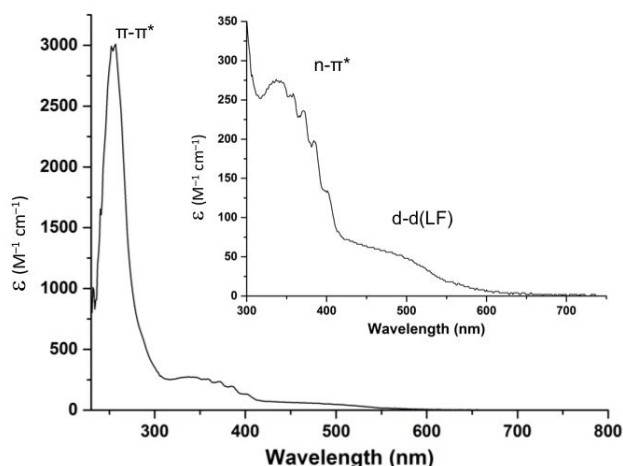
Scheme 1 illustrates the sequence used to prepare these two new compounds. The *cis*-dichlorido complex  $\text{cis-[Cr(PetA)Cl}_2\text{]Cl}$  is an isolable minor biproduct of the synthesis of the *trans*- analog (see the Supporting Information for more details). The X-ray crystal structure of the  $\text{trans-Cr(PetA)(ONO)}_2^+$  cation is displayed in Figure 1 and the unit cell structure of the  $\text{trans-[Cr(PetA)(ONO)}_2\text{]BF}_4$  salt is shown in SI Figure S5. The unit cell structure of  $\text{trans-[Cr(PetA)Cl}_2\text{]Cl}$  is shown in SI Figure S6. Data (crystal and structural refinement data, atomic coordinates plus bond lengths and angles) from the crystal structure determinations of these two compounds and for  $\text{cis-[Cr(PetA)Cl}_2\text{]Cl}$  are summarized, respectively, in SI Tables S1, S2 & S3. The Cl-Cr-Cl angles for the *cis*- and *trans*-dichlorido complexes are 88.8° and 180.0°, respectively. The electronic spectrum of PetACrONO is shown in Figure 2.



**Figure 1.** Structure (thermal ellipsoids at 50% probability, H atoms omitted for clarity) of one of two  $\text{trans-Cr(PetA)(ONO)}_2^+$  cations in the independent unit determined by x-ray diffraction of  $[\text{trans-Cr(PetA)(ONO)}_2]\text{BF}_4$  recrystallized from dichloromethane (DCM). One DCM molecule of crystallization was also found in this unit (see packing diagram, SI Figure S5). The bond lengths and angles for both cations are provided in the Supporting information (Table S1).

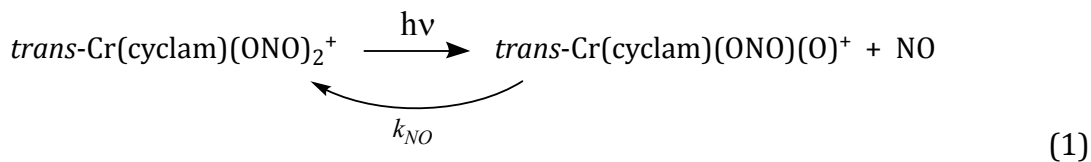
***Solution phase photochemical reactions.*** The solution phase photolysis of  $\text{trans-[Cr(PetA)(ONO)}_2\text{]BF}_4$  was examined using the Sievers NOA to evaluate the photo-lability of this

photoNORM toward NO release. The NOA determines with high sensitivity and precision the NO that is swept from the photolysis solution with an entraining gas (either He or medical grade



**Figure 2.** Absorption spectrum of  $[trans\text{-Cr(PetA)(ONO)}_2]\text{BF}_4$  in acetonitrile solution. The  $\lambda_{\text{max}}(\epsilon)$  values are 257 nm ( $3,008 \text{ M}^{-1} \text{ cm}^{-1}$ ) 337 nm ( $276 \text{ M}^{-1} \text{ cm}^{-1}$ ) and 491 nm ( $51 \text{ M}^{-1} \text{ cm}^{-1}$ )

air). For PetACrONO, photo-activated NO release was readily apparent as has been shown previously for the photolysis of  $trans\text{-Cr(cyclam)(ONO)}_2^+$  ("CrONO", cyclam = 1,4,8,11-tetraazacyclotetradecane). Earlier studies showed CrONO to undergo reversible CrO–NO bond homolysis to give NO plus a Cr(IV) intermediate (eq. 1) that can be trapped by various oxidants or reductants.<sup>43</sup> Quantum yields of NO release ( $\Phi_{\text{NO}}$ ) were relatively insensitive to excitation wavelength over the range 365–436 nm with values in the range 0.18–0.28 over various conditions.<sup>44</sup> Photolysis at 546 nm gave comparable photochemistry, despite the very low extinction coefficients at this wavelength.



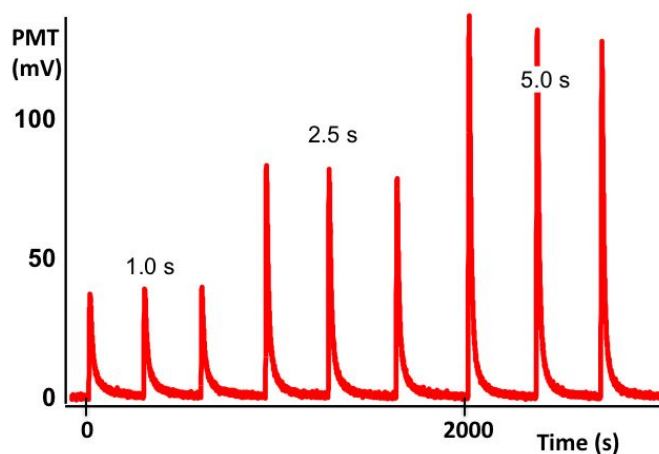
Similarly, 451 nm photolysis of an iso-butyronitrile solution of PetACrONO (0.5 mM) led to NO release as detected with the NOA. Medical grade air was the entraining gas and quantitative analysis of the NO released during short defined photolysis intervals gave a  $\Phi_{\text{NO}}$  value of  $0.32 \pm 0.01$  (Figure S3), indicating that the photochemistry and photolability of the *trans*-

Cr(PetA)(ONO)<sub>2</sub><sup>+</sup> cation are comparable to those of CrONO itself.<sup>44</sup> Thus, the introduction of phenyl and/or methyl groups to the cyclam ring and switching to a less polar medium did not inhibit the overall photolability of PetACrONO toward NO release. Analogous photolysis of PetACrONO in acetonitrile solvent using 365 nm excitation gave a similar result ( $\Phi_{\text{NO}} = 0.30 \pm 0.01$ ).

**Visible range photochemistry of loaded polymer disks.** The above experiments demonstrated that **1** is photolabile toward NO release in fluid media. However, the question remains whether this photolability would lead to ready NO release from the PDs infused with PetACrONO. To address this point, a series of PDs were prepared from different commercial silicone-based polymer formulations (NuSil) and were infused with PetACrONO using the highly self-consistent procedures described in the Experimental Section. The silicone polymers used to fabricate the PDs are proprietary, commercial formulations currently in use for *in vivo* biomedical applications. These proprietary biocompatible formulations may include different quantities of monomers, cross-linkers, resins, silica, processing aids, fillers, inhibitors, and catalysts that are designed to control desired properties such as appearance, optical clarity, viscosity, specific gravity, tensile and tear strengths, gas permeability, etc. In all the cases, the polymer disks appeared to be optically clear or translucent.

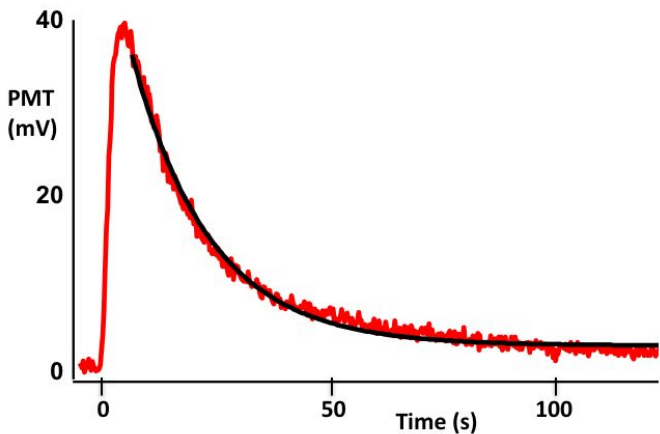
Photolysis studies were carried out using visible light excitation with a royal blue LED operating at 451 nm for PDs loaded only with [*trans*-Cr(PetA)(ONO)<sub>2</sub>]<sub>2</sub>BF<sub>4</sub> or using NIR excitation with a diode laser operating at 794 nm for PDs loaded both with this photoNORM and with the Nd-UCNPs. Figure 3 illustrates the NOA signals recorded for the 451 nm LED photolysis of a PetACrONO infused PD prepared from NuSil Technology Med-6233 for excitation times of 1.0, 2.5 and 5.0 s at 45 mW. The integrated signals provide a quantitative evaluation of the NO released in each case, the average values being  $119 \pm 9$ ,  $193 \pm 4$  and  $272 \pm 10$  picomoles, respectively. Although the longer photolysis times led to larger integrated signals, the increase was not linear. This non-linearity may reflect the reversibility of the photoreaction in analogy to eq. 1. Given that diffusion of NO out of the polymer is relatively slow (see below), the back reaction with the Cr(IV) oxo intermediate as in eq. 1 may deplete the net amount of NO released from the PD and thus lower the photochemical efficiency. A similar pattern was observed for 451

nm photolyses of PDs prepared from the other silicone formulations infused with [*trans*-Cr(PetA)(ONO)<sub>2</sub>]<sub>2</sub>BF<sub>4</sub> (SI Table S4). In addition, successive experiments, showed a modest decrease in the quantity of NO released, suggesting some depletion of the PetACrONO substrate.



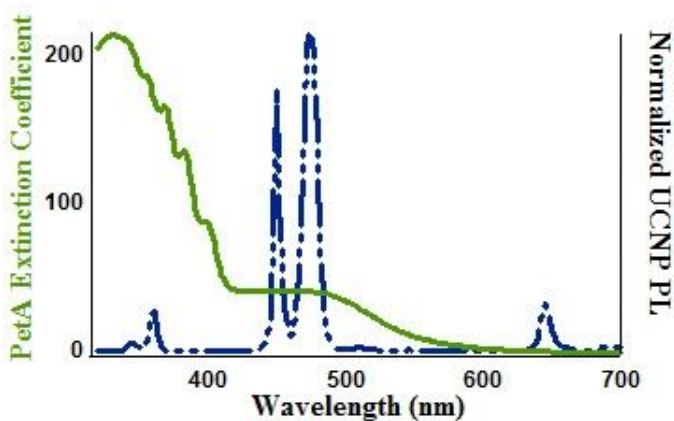
**Figure 3.** NOA data for 451 nm photolysis (45 mW) of silicone MED-6233 infused with [*trans*-Cr(PetA)(ONO)<sub>2</sub>]<sub>2</sub>BF<sub>4</sub> for photolysis intervals of 1.0, 2.5, and 5.0 s. The net amount of NO released from the disk was calculated from the integrated NOA signals.

Close examination of the individual signals shown in Figure 3 indicates that upon 451 nm excitation of the infused PD for a period from 1.0 to 5.0 s, there is a rise of the NOA signal for several seconds, reflecting in part the response time of the apparatus shown in Figure S1. This is followed by a decay of the signal that fits reasonably well to a single exponential decay function (Figure 4). For example, the NOA signal decay subsequent to a 1.0 s irradiation of PetACrONO infused in a Med-6233 PD displayed an average lifetime ( $\tau_{\text{decay}}$ ) of  $17.0 \pm 0.3$  s (Figure 4) and this was reproducible for subsequent 1 s excitations within the experimental uncertainty given. Similar decays were observed for the 2.5 and 5.0 s irradiation periods of the same sample, although the fits gave somewhat smaller values of  $\tau_{\text{decay}}$ ,  $14.1 \pm 0.2$  and  $12.3 \pm 0.1$  s, respectively. As would be expected, these decay properties are a property of the specific silicone formulation utilized to prepare the PDs, although the differences in the calculated  $\tau_{\text{decay}}$  values are not dramatic. These data are presented in SI Figures S7-S9 and SI Table S5, with  $\tau_{\text{decay}}$  ranging from 14 to 28 s with samples excited for 1.0 s and with similar ranges ( $\sim 12$ -22 s and  $\sim 11$ -19 s, respectively) for excitation times of 2.5 s and of 5.0 s.



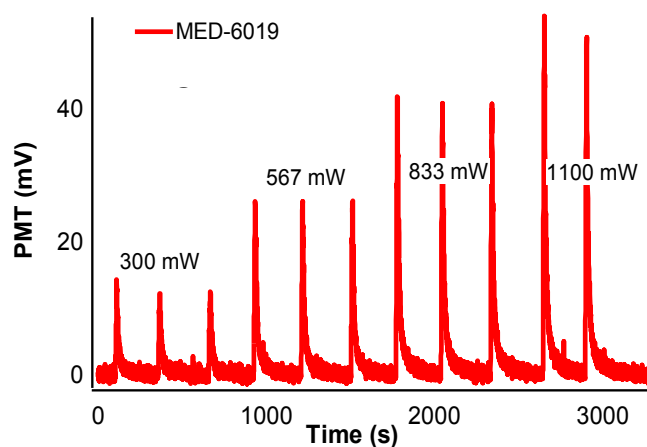
**Figure 4.** Temporal signal from the NOA upon 451 nm photolysis, of the PetACrONO in a silicone MED-6233 PD for 1.0 s showing a fit of the signal decay of the NOA signal fit to a first order exponential.

**NIR photochemistry of loaded polymer disks.** Figure 5 demonstrates the overlap between the emission from Nd-UCNPs upon 794 nm excitation and the absorption spectrum of PetACrONO. The upconverted visible emission from these Nd-UCNPs is readily apparent in SI Figure S10, which illustrates the result of passing a beam of 794 nm light through a hexane solution containing this material. PDs from single polymer formulation, NuSil Technology Med-6019, were used for these studies given the relatively modest differences in the photochemical properties of the PetACrONO loaded PDs summarized in SI Tables S4 and S5.



**Figure 5.** Comparison of the absorption spectrum of *trans*-[Cr(PetA)(ONO)<sub>2</sub>]BF<sub>4</sub> in acetonitrile (green line) to the photoluminescence spectrum of the Nd/Tm-UCNP: β-NaYF<sub>4</sub>:Tm/Nd/Yb/Gd-(0.5/1.0/30/20 %)/NaGdF<sub>4</sub>:Tm(20 %) upon 794 nm excitation with the laser power 1100 mW (blue).

Figure 6 displays the NOA signals observed upon 794 nm excitation of Med-6019 PDs loaded with PETACrONO and with the Nd-UCNPs. NO release that increases with increasing laser power is readily apparent. The averaged integrated NOA signals demonstrate the release of 26.4, 56.6, 88.7 and 110.3 picomoles of NO for excitation at 300, 567, 833 and 1100 mW, respectively. No nitric oxide was released upon 794 nm irradiation of a PD loaded only with PETACrONO, so this behavior can readily be attributed to the presence of the Nd-UCNPs. The NO release proved to be almost linear with the laser power employed, and this proved somewhat unexpected given the non-linear behavior seen for aqueous solutions containing the photoNORM RBS ( $\text{Na}[\text{Fe}_4\text{S}_3(\text{NO})_7]$ ) and silica coated  $\text{NaYF}_4:\text{Yb}/\text{Er}@\text{NaYF}_4$  core/shell UCNPs that are activated with 980 nm excitation.<sup>39</sup> However, as noted above, direct excitation at 451 nm did not respond linearly to irradiation time, and this was attributed to enhanced back reactions when more NO was generated in a single event. Thus, two counteracting trends may be at play in the present case.



**Figure 6** NOA signals for 10 s photolyses of *trans*-[Cr(PetA)(ONO)<sub>2</sub>]BF<sub>4</sub> infused into a MED-6019 PD at 794 nm with different diode laser powers.

### Summary:

In these studies, we report the synthesis and characterization of a new lipid soluble photoNORM, the chromium(III) O-nitrito complex salt *trans*-[Cr(PetA)(ONO)<sub>2</sub>]BF<sub>4</sub>. Visible light excitation of silicone polymer disks prepared from various biocompatible commercial formulations triggers the release of NO in quantities determined by the length of the excitation

pulse. Thus, photo-uncaging from such an implantable device allows one to define the location, timing and dosage for the release of this potent bioregulator. However, with the exception of a subcutaneous implant, such a device would need to be attached to an optical fiber owing to the relatively poor tissue transmission of visible light. To address this issue, we also report that including neodymium-doped  $\beta$ -NaYF<sub>4</sub>:Tm/Nd/Yb/Gd@NaYF<sub>4</sub>:Nd upconverting nanoparticles in the polymer disk allows the use of much more penetrating NIR wavelengths at  $\sim$ 800 nm as the excitation source. NIR photoexcitation of these UCNPs leads to the emission of upconverted visible light and activates NO release from the photoNORM. The mechanism of such photosensitization has not been determined, although it is likely that this occurs by "trivial" energy transfer, namely the emission of light from the UCNP followed by reabsorption by the photoNORM.

The above studies represent a continuation of our earlier demonstration of NO uncaging by 980 nm photoexcitation of poly(dimethylsiloxane) PDs containing the RBS as the photoNORM and  $\beta$ -NaYF<sub>4</sub>:Er/Yb/Gd@NaYF<sub>4</sub> UCNPs as the NIR activator.<sup>33</sup> Although, the latter investigation showed that such NIR photoactivation could indeed be effected through tissue filters, the inclusion of Nd<sup>3+</sup> in the core and shell of the Nd-UCNPs used here allows the application of 794 nm excitation and thus avoids potential heat damage owing to the modest absorbance by water at 980 nm.<sup>42</sup>

We had anticipated that the different commercial formulations of the silicone polymers might lead to considerable differences in performance with regard to NO uncaging. However, the differences are relatively small, with both the quantity and  $\tau_{\text{decay}}$  for NO release upon a short term (e.g., 1 s) excitation varying only about a factor of two for the various formulations (SI Tables S4 & S5). This similarity may in part be due to each of these formulations being silicone-based, but also is likely the result of the photoNORM being infused into preformed PDs as opposed to being co-dissolved prior to the gelling process. As a result, this precursor is located at readily accessible sites where NO once uncaged can diffuse to the surface. In contrast, Ostrowski and coworkers prepared similarly sized films of composites but dissolved their photoNORM in the polymers prior to curing resulting in marked differences in release efficiencies depending on the gas permeabilities of the materials involved.<sup>30</sup>

## ASSOCIATED CONTENT

**Supporting Information:** Included are detailed procedures for the syntheses of the PetA chromium(III) complexes and for the preparation of polymer disks; crystal structure details for *trans*-[Cr(PetA)(ONO)<sub>2</sub>]BF<sub>4</sub>, *trans*-[Cr(PetA)Cl<sub>2</sub>]Cl and *cis*-[Cr(PetA)Cl<sub>2</sub>]Cl as well as 10 figures and 6 tables of supporting information. Also available are CIF files for the three crystal structures reported. The Supporting Information is available free of charge on the ACS Publications website at DOI: .....

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### Notes:

The authors declare no competing financial interests.

## Funding Sources

This work was supported in part by the Chemistry Division of the National Science Foundation (Grants CHE-1405062 and CHE-1565702).

## ACKNOWLEDGEMENTS

We thank the Molecular Foundry User Program and especially Dr. Emory Chan and Elizabeth S. Levy of the Molecular Foundry (supported by the Office of Science, Office of Basic Energy Sciences, U.S. Department of Energy under Contract no. DE-AC02-05CH11231) for the synthesis of UCNPs. J.V.G. thanks the PIRE-ECCI (Grant NSF-OISE-0968399) program at UCSB for graduate fellowships. We thank Dr. Jerry Macala of Allergan Medical and Jack Lambert of NuSil Technology for providing medical grade silicone formulations and for technical assistance. Bruce Dunson of UCSB fabricated molds to make silicone disks and Richard Bock helped design and build glassware for the photolysis apparatus.



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